

Adipokines and Insulin Resistance

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Obesity is associated with an array of health problems in adult and pediatric populations. Understanding the pathogenesis of obesity and its metabolic sequelae has advanced rapidly over the past decades. Adipose tissue represents an active endocrine organ that, in addition to regulating fat mass and nutrient homeostasis, releases a large number of bioactive mediators (adipokines) that signal to organs of metabolic importance including brain, liver, skeletal muscle, and the immune system—thereby modulating hemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis. In the present review, we summarize current data on the effect of the adipose tissue-derived hormones adiponectin, chemerin, leptin, omentin, resistin, retinol binding protein 4, tumor necrosis factor- α and interleukin-6, vaspin, and visfatin on insulin resistance.

Online address: <http://www.molmed.org>

doi: 10.2119/2008-00058.Rabe

INTRODUCTION

Adipose tissue is composed of adipocytes embedded in a loose connective tissue meshwork containing adipocyte precursors, fibroblasts, immune cells, and various other cell types. Adipose tissue was traditionally considered an energy storage depot with few interesting attributes. Due to the dramatic rise in obesity and its metabolic sequelae during the past decades, adipose tissue gained tremendous scientific interest. It is now regarded as an active endocrine organ that, in addition to regulating fat mass and nutrient homeostasis, releases a large number of bioactive mediators (adipokines) modulating hemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis. Table 1 summarizes the adipokines discussed in this review article, the interplay between adipokines, and their effects on glucose homeostasis.

ADIPONECTIN

Adiponectin expression occurs from an intermediate stage of adipogenesis

onwards (1,2), and represents the most abundant protein secreted by adipose tissue. Unlike most other adipokines, plasma adiponectin levels were reduced in animal models of obesity and insulin resistance (2,3). Administration of recombinant adiponectin to rodents resulted in increased glucose uptake and fat oxidation in muscle, reduced hepatic glucose production, and improved whole-body insulin sensitivity (4–6). Adiponectin transgenic mice showed partial amelioration of insulin resistance and diabetes (7) and suppression of endogenous glucose production (8). In contrast, adiponectin-deficient mice exhibited insulin resistance and glucose intolerance (9–11). In addition to its insulin-sensitizing effects, adiponectin may alter glucose metabolism through stimulation of pancreatic insulin secretion *in vivo* (12). Apart from its peripheral actions, adiponectin was shown to modulate food intake and energy expenditure during fasting (increased food intake and reduced energy expenditure) and refeeding (opposite effects)

through its effects in the central nervous system (13).

In humans, plasma adiponectin levels were correlated negatively with adiposity (14–17), insulin resistance (16,18,19), type 2 diabetes (16,20), and metabolic syndrome (21–23), yet positively correlated with markers of insulin sensitivity in frequently sampled intravenous glucose tolerance testing (17,24,25) and clamp studies (15,19). Prospective and longitudinal studies indicated that lower adiponectin levels were associated with a higher incidence of type 2 diabetes (26–33). Adiponectin single nucleotide polymorphisms (SNPs) have been associated variably with increased body mass index (BMI), insulin resistance-related traits, and type 2 diabetes (34). However, in a systematic meta-analysis of all published data on adiponectin SNPs, only the +276G→T variant was a strong determinant of insulin resistance with minor allele homozygotes having a lower homeostasis model assessment of insulin resistance index than carriers of other genotypes. No consistent effect on BMI or risk of type 2 diabetes was observed (34).

Adiponectin circulates in plasma as a low-molecular weight trimer, a middle-molecular weight hexamer, and high-molecular weight (HMW) 12- to 18-mer, and these forms were postulated to differ in biologic activity (35,36). HMW adi-

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Table 1. Adipokines, adipokine interplay and the effects on glucose homeostasis^a

Adipokine	Receptor	Effects on other adipokines	Metabolic function
Adiponectin	AdipoR1, AdipoR2, T-cadherin	Suppression of TNF- α and IL-6 expression	Suppression of hepatic gluconeogenesis Stimulation of fatty acid oxidation in liver and skeletal muscle Stimulation of glucose uptake in skeletal muscle Stimulation of insulin secretion Modulation of food intake and energy expenditure
Chemerin	CMKLR1	Suppression of TNF- α and IL-6 expression Stimulation of adiponectin expression	Enhancement of insulin-stimulated glucose uptake and IRS-1 phosphorylation in 3T3-L1 adipocytes
Leptin	LR isoforms α - β ^b	Stimulation of TNF- α and IL-6 expression Suppression of resistin and retinol binding protein 4 expression Stimulation of adiponectin expression	Repression of food intake Promotion of energy expenditure Stimulation of fatty acid oxidation in liver, pancreas and skeletal muscle Modulation of hepatic gluconeogenesis Modulation of pancreatic β -cell function
Omentin	Unknown	Unknown	Enhancement of insulin-stimulated glucose transport and Akt phosphorylation in human adipocytes
Resistin	Unknown	Stimulation of TNF- α and IL-6 expression	Induction of insulin resistance in mice Lack of a clear function in glucose metabolism in humans
Retinol binding protein 4	unknown (RAR, RXR, cell surface receptors?)	Unknown	Stimulation of hepatic gluconeogenesis in mice Impairment of skeletal muscle insulin signaling in mice Uncertain effect on insulin resistance in humans
Tumor necrosis factor- α and IL-6	TNFR, IL-6R/gp130	Stimulation of leptin, resistin, and visfatin/PBEF/Nampt expression Suppression of adiponectin and retinol binding protein 4 expression	Modulation of hepatic and skeletal muscle insulin signaling
Vaspin	— ^c	Suppression of leptin, resistin, and TNF- α expression Stimulation of adiponectin expression	Improvement of insulin sensitivity in mice Uncertain effect on insulin sensitivity in humans
Visfatin/PBEF/Nampt	— ^d	Stimulation of TNF- α and IL-6 expression	Stimulation of insulin secretion in mice Uncertain effect on insulin resistance in rodents and humans

^aAbbreviations in table: AdipoR1, adiponectin receptor 1; AdipoR2, adiponectin receptor 2; CMKLR1, chemokine like receptor-1; IL-6R, interleukin-6 receptor; IRS-1, insulin receptor substrate-1; LR, leptin receptor; Nampt, nicotinamide phosphoribosyltransferase; PBEF, pre-B cell colony-enhancing factor; RAR, retinoic acid receptor; RXR retinoic acid-X receptor; TNFR, Tumor necrosis factor- α receptor; vaspin, visceral adipose tissue-derived serine protease inhibitor.

^bLRb is restricted to the hypothalamus, brainstem and key regions of the brain which control feeding, energy balance and glucose metabolism.

^cEffects likely to be mediated through inhibition of a yet-unknown protease.

^dEffects mediated through nicotinamide adenine dinucleotide biosynthetic activity.

ponectin was proposed to be the biologically active form of the hormone (37), and, although not unchallenged (38), was shown to be superior to total adiponectin in predicting insulin resistance and the metabolic syndrome trait cluster (39–41). Adiponectin expression and secretion was demonstrated to be upregulated by thiazolidinediones (TZDs) (42–44), and HMW adiponectin is the predominant form of adiponectin increased by TZDs (37).

Adiponectin's effects on glucose metabolism are mediated through two distinct receptors termed adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2). AdipoR1 is expressed ubiquitously, whereas AdipoR2 is expressed most abundantly in the liver (45). Similar to adiponectin, expression of both receptors was decreased in mouse models of obesity and insulin resistance (46,47). Yamauchi *et al.* (47) reported that liver-specific adenoviral expression of AdipoR1 in leptin-receptor deficient db/db mice resulted in activation of 5'AMP-activated protein kinase (AMPK), leading to reduced expression of genes encoding hepatic gluconeogenic enzymes such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase 1, and of genes encoding molecules involved in lipogenesis, such as sterol regulatory element-binding protein 1c. Hepatic expression of AdipoR2 increased expression of genes involved in hepatic glucose uptake such as glucokinase, and of peroxisome proliferator-activated receptor- α (PPAR- α) and its target genes such as acyl-CoA oxidase and uncoupling protein 2. Activation of AMPK reduced endogenous hepatic glucose production, while expression of both receptors increased fatty acid oxidation, decreased hepatic triglyceride content and improved insulin resistance. Conversely, targeted disruption of AdipoR1 resulted in the abrogation of adiponectin-induced AMPK activation, and in increased endogenous glucose production and insulin resistance. Knockout of AdipoR2 caused decreased activity of PPAR- α signaling pathways and insulin resistance.

Simultaneous disruption of both AdipoR1 and AdipoR2 abolished adiponectin binding and actions, resulting in increased glucose intolerance and insulin resistance compared with the single knockout models (47). The role of T-cadherin, another putative adiponectin receptor (48), in adiponectin signaling appeared to be minor since, in contrast to control mice, administration of adiponectin to AdipoR1/R2 double knockout mice did not improve plasma glucose levels (47). The impact of AdipoR1 and AdipoR2 on glucose metabolism in rodents has been examined by two more studies with, in part, conflicting results. Bjursell *et al.* (49) reported that AdipoR1 knockout mice showed increased adiposity associated with decreased glucose tolerance, reduced spontaneous locomotor activity, and decreased energy expenditure. Unexpectedly, however, AdipoR2 deficient mice were lean and resistant to high fat diet-induced obesity associated with improved glucose tolerance and increased spontaneous locomotor activity and energy expenditure. Consistent with these data, Liu *et al.* (50) demonstrated that disruption of AdipoR2 diminished high fat-induced insulin resistance and reduced plasma glucose levels in leptin-deficient ob/ob mice. However, glucose homeostasis in these animals on long-term high fat diet deteriorated because of failure of pancreatic β -cells to compensate for the moderate insulin resistance.

In humans, data regarding a possible association of adiponectin receptor expression in adipose tissue or skeletal muscle and obesity or insulin resistance were highly divergent and dependent on the population studied (51–59). Furthermore, although polymorphisms in both adiponectin receptor genes have been found to be associated with insulin resistance and type 2 diabetes (34,60), these associations have not been replicated widely across populations. Thus, the number of studies available to date is still too small to draw firm conclusions on the role of variability in AdipoR1 and/or AdipoR2 expression in predicting insulin resistance and related disorders.

In summary, adiponectin is an abundantly expressed adipokine that exerts a potent insulin-sensitizing effect through binding to its receptors AdipoR1 and AdipoR2, leading to activation of AMPK, PPAR- α , and presumably other yet-unknown signaling pathways. In obesity-linked insulin resistance, both adiponectin and adiponectin receptors are downregulated. Upregulation of adiponectin/adiponectin receptors or enhancing adiponectin receptor function may represent an interesting therapeutic strategy for obesity-linked insulin resistance.

CHEMERIN

Chemerin (RARRES2 or TIG2) is a recently discovered chemokine (61) highly expressed in liver and white adipose tissue (62,63). It exerts potent antiinflammatory effects on activated macrophages expressing the chemerin receptor CMKLR1 (chemokine-like receptor-1) in a cysteine protease-dependent manner (64). Furthermore, chemerin is crucial for normal adipocyte differentiation and modulates the expression of adipocyte genes involved in glucose and lipid homeostasis, such as glucose transporter-4, fatty acid synthase, and adiponectin via its own receptor (62,63,65). In 3T3-L1 adipocytes, chemerin was reported to enhance insulin-stimulated glucose uptake and insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation, suggesting that chemerin may increase insulin sensitivity in adipose tissue (66). Conflicting data exist regarding the association of chemerin with obesity and diabetes in rodents. Chemerin expression was shown to be decreased in adipose tissue of db/db mice compared with controls (66). In contrast, chemerin expression was significantly higher in adipose tissue of impaired glucose tolerant and diabetic *Psammomys obesus* compared with normal glucose tolerant sand rats (62). In humans, chemerin levels did not differ significantly between subjects with type 2 diabetes and normal controls. However, in normal glucose tolerant subjects, chemerin levels were asso-

ciated significantly with BMI, triglycerides, and blood pressure (62). Further studies are needed to determine the physiological role of chemerin in glucose metabolism, and to identify chemerin's target tissues as well as relevant signal transduction pathways.

LEPTIN

Since its identification in 1994, leptin has attracted much attention as one of the most important signals for the regulation of food intake and energy homeostasis (67–69). Hypothalamic as well as brain stem nuclei play a critical role in integrating the information on absorbed food, on the amount of energy stored in the form of fat and on blood glucose levels to regulate feeding, energy storage, or expenditure. Leptin receptor activation at these sites leads to repression of orexigenic pathways (for example, those involving neuropeptide Y [NPY] and agouti-related peptide [AgRP]) and induction of anorexigenic pathways (such as those involving pro-opiomelanocortin [POMC] and cocaine and amphetamine-regulated transcript [CART]) via Janus kinase (JAK)-signal transducers and activators of transcription (STAT) and IRS/phosphoinositide-3 kinase (PI3K) signaling (70). Although changes in food intake and total body fat clearly can affect insulin sensitivity in peripheral tissues, several observations suggested that leptin regulation of glucose homeostasis occurs independently of its effects on food intake through central and peripheral mechanisms. Hypothalamic arcuate nucleus (ARC)-specific expression of leptin receptor in leptin receptor-deficient mice resulted in a modest reduction of food intake and body fat mass, yet normalized blood glucose and insulin levels (71). ARC-specific restoration of leptin receptor in obese, leptin receptor-deficient Koletsky rats markedly improved insulin sensitivity via a mechanism that was not dependent on reduced food intake, but was attenuated by intraventricular infusion of a PI3K inhibitor (72). ARC-directed expression of a constitutively active mutant of protein kinase B,

an enzyme activated by PI3K, mimicked the insulin-sensitizing effect of restored hypothalamic leptin signaling in these animals. In contrast, mice with a mutant leptin receptor that cannot signal via the JAK-STAT pathway, yet otherwise functions normally, developed severe hyperphagia and obesity, but unlike leptin receptor-deficient mice, exhibited only mild disturbances of glucose homeostasis that can be prevented by caloric restriction (73). These results suggested that although leptin receptor-mediated JAK-STAT signaling is essential for regulation of food intake and body weight, leptin-stimulated PI3K signaling appears to be important for regulation of glucose metabolism. Leptin also limits accumulation of triglycerides in liver and skeletal muscle through a combination of direct activation of AMPK and indirect actions mediated through central neural pathways, thereby improving insulin sensitivity (74,75). Furthermore, leptin modulates pancreatic β -cells function through direct actions (76,77) and indirectly through central neural pathways (78,79). Leptin was shown to inhibit insulin secretion in lean animals. As body weight increased, leptin signaling protected the β -cell from adverse effects of overnutrition such as lipid accumulation, thus improving β -cell function (77). Insulin stimulates both leptin biosynthesis and secretion from adipose tissue establishing a classic endocrine adipo-insular feedback loop; the so-called “adipo-insular axis” (80).

The concept of “leptin resistance” was introduced when increased adipose leptin production was observed in the majority of obese individuals without adequate leptin-mediated end-organ response (81). Leptin improves glucose homeostasis in humans with lipodystrophy or congenital leptin deficiency (82,83). However, results in humans with ‘typical’ obesity were disappointing in this regard (84). Studies in obese rodents suggested that leptin resistance is associated with impairment of leptin transport across the blood-brain-barrier (BBB), reduction of leptin-mediated JAK-STAT

signaling, and induction of suppressor of cytokine signaling-3 (SOCS-3) (81,85). Attenuation of leptin sensitivity in the brain leads to excess triglyceride accumulation in adipose tissue, as well as muscle, liver, and pancreas, resulting in impaired insulin sensitivity and secretion (86). The concept of “leptin resistance” has been challenged recently by an alternate concept of “hypothalamic leptin insufficiency.” The major tenet of this postulation is that BBB restricts the blood-to-brain entry of leptin in response to hyperleptinemia resulting in leptin insufficiency at multiple target sites in the brain (87).

In summary, leptin serves as a major ‘adipostat’ by repressing food intake and promoting energy expenditure. Independent of these effects, leptin improves peripheral (hepatic and skeletal muscle) insulin sensitivity and modulates pancreatic β -cell function. In the majority of cases of obesity, despite both an intact leptin receptor and high circulating leptin levels, leptin fails to induce weight loss. This diminished response to the anorexigenic and insulin-sensitizing effects of leptin is called “leptin resistance.”

OMENTIN

Omentin is a fat depot-specific secretory protein synthesized by visceral stromal vascular cells, but not adipocytes. Omentin enhanced insulin-stimulated glucose transport and Akt phosphorylation in human subcutaneous and visceral adipocytes, suggesting that omentin may improve insulin sensitivity (88). Plasma omentin-1 levels, the major circulating isoform in human plasma, were correlated inversely with obesity and insulin resistance as determined by homeostasis model assessment yet correlated positively with adiponectin and HDL levels (89). Administration of glucose and insulin to human omental adipose tissue explants resulted in a dose-dependent reduction of omentin-1 expression. Furthermore, prolonged insulin-glucose infusion in healthy individuals resulted in significantly decreased plasma omentin-1

levels (90). The physiological role of omentin in glucose metabolism, omentin's target tissues, a receptor, or relevant signal transduction pathways still need to be determined.

RESISTIN

Resistin, a member of the resistin-like molecule (RELM) family of cysteine-rich proteins, has a controversial history regarding its role in the pathogenesis of obesity-mediated insulin resistance and type 2 diabetes. Resistin was discovered in 2001 as a TZD-downregulated gene in mouse adipocytes (91). In rodents, circulating levels of resistin were increased in obesity (92), and both gain- (91,93–96) and loss-of-function studies (91,97–99) demonstrated a role for resistin in mediating hepatic or skeletal muscle (depending on the animal model) insulin resistance (94,95,97,98). There is considerable controversy about the role of resistin in humans. Human resistin is produced and secreted mainly by peripheral-blood mononuclear cells (100). Human studies over the past years reported contradictory findings with regards to a physiological role for resistin in glucose metabolism. Several groups suggested resistin levels and SNPs to be associated with obesity, insulin resistance, and type 2 diabetes (19,101–106). However, other groups failed to identify changes in resistin levels or SNPs in these conditions (107–114). Although a clear function for resistin in glucose metabolism in humans is still lacking, data indicate that resistin has a role in inflammatory processes. The expression of resistin in human peripheral-blood mononuclear cells is upregulated by the proinflammatory cytokines tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) (115). Conversely, resistin induced the expression of TNF- α and IL-6 in white adipose tissue and in peripheral-blood mononuclear cells (116–118). Plasma resistin levels were reported to be associated with many inflammatory markers including C-reactive protein (119), soluble TNF- α receptor-2, IL-6, and lipoprotein-associated phospholipase A2 (120) in several pathophysi-

ological conditions. Resistin was shown to be associated with disease activity in patients with inflammatory bowel disease (121), to correlate with severity of disease in severe sepsis and septic shock (122), and to be associated with coronary artery disease (120). Furthermore, resistin may be involved in the pathogenesis of rheumatoid arthritis (117). Considering the crosstalk between inflammatory pathways and the insulin signaling cascade (see below “Tumor necrosis factor- α and interleukin-6”), resistin may represent a link between inflammation and metabolic signals (123).

RETINOL BINDING PROTEIN 4

A potential link between retinol binding protein 4 (RBP4) and type 2 diabetes was suggested by Yang *et al.* (124) reporting that RBP4 was elevated in insulin-resistant adipose specific GLUT4 knockout mice and humans with obesity and type 2 diabetes. Transgenic overexpression of human RBP4 in wildtype mice or administration of recombinant RBP4 to wildtype mice was shown to cause insulin resistance through induction of hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase and impairment of skeletal muscle insulin signaling. In contrast, genetic deletion of RBP4 enhanced insulin sensitivity. The effects of RBP4 may be mediated through retinol-dependent (via retinoic acid receptors [RARs] and retinoic acid-X receptors [RXRs] to regulate gene transcription) or retinol-independent mechanisms (for example, interaction with cell surface receptors such as Megalin/gp320). Serum RBP4 concentrations were elevated in insulin-resistant humans with obesity, impaired glucose tolerance and type 2 diabetes, and even in lean normoglycemic subjects with a strong family history of type 2 diabetes (124,125). A large number of subsequent studies confirmed an association of increased circulating RBP4 levels with various aspects of adiposity (126–129), insulin resistance (128,130–133), type 2 diabetes (127,134,135) and the metabolic syndrome (136). Improving insulin sensi-

tivity by interventions such as exercise training, lifestyle modification, or gastric banding surgery reduced serum RBP4 levels in humans (125,126,137,138). Genetic studies reported an association of RBP4 SNPs and insulin resistance, impaired insulin secretion, and/or type 2 diabetes (139,140). Other studies, however, failed to establish an association of RBP4 levels with obesity (141–143), insulin resistance (141–144), type 2 diabetes (144) or components of the metabolic syndrome (145). This discrepancy may be explained in part through methodological differences in the measurement of RBP4 (146) as well as differences in the study populations.

Based on current data, the function of RBP4 as an adipokine exerting metabolic effects in glucose metabolism in humans remains uncertain and might be restricted to rodent models (147).

TUMOR NECROSIS FACTOR- α AND INTERLEUKIN-6

Both TNF- α and IL-6, the most widely studied cytokines produced by adipose tissue, were reported to modulate insulin resistance. Evidence supporting a key role for TNF- α in obesity-related insulin resistance came from studies showing that deletion of TNF- α or TNF- α receptors resulted in significantly improved insulin sensitivity in both diet-induced obese mice and leptin-deficient ob/ob mice (148). In humans, adipose tissue TNF- α expression correlated with BMI, percentage of body fat, and hyperinsulinemia, whereas weight loss decreased TNF- α levels (149). Fasting TNF- α plasma levels were associated with insulin resistance in the Framingham Offspring Study (19). Neutralization of TNF- α improved insulin resistance in obese rats (150). However, infusion of TNF- α -neutralizing antibodies to obese, insulin-resistant subjects, or type 2 diabetic patients, did not improve insulin sensitivity (151,152).

Conflicting data exist regarding the role of IL-6 in insulin resistance (153, 154). IL-6 was reported to reduce insulin-dependent hepatic glycogen syn-

thesis (155,156) and glucose uptake in adipocytes (157), whereas insulin-dependent glycogen synthesis and glucose uptake was enhanced in myotubes (158,159). The effect of IL-6 on hepatic glucose production is still under debate (160,161). Kim *et al.* (160) reported that IL-6 infusion in mice blunted insulin's ability to suppress hepatic glucose production. In contrast, Inoue *et al.* (161) demonstrated that intraventricular insulin infusion resulted in IL-6-mediated suppression of hepatic gluconeogenesis. Overall, circulating IL-6 levels are increased in obese and insulin resistant subjects (162,163). One may speculate that persistent systemic increases of IL-6 in states of chronic inflammation such as obesity and type 2 diabetes may trigger insulin resistance, whereas transient increases may contribute to normal glucose homeostasis. TNF- α and IL-6 modulate insulin resistance through several distinct mechanisms, including c-Jun N-terminal kinase 1 (JNK1)-mediated serine phosphorylation of IRS-1, I κ B kinase (IKK)-mediated nuclear factor- κ B (NF- κ B) activation, and induction of SOCS-3 (164).

VASPIN

Visceral adipose tissue-derived serine protease inhibitor (vaspin) was identified in visceral adipose tissue of Otsuka Long-Evans Tokushima fatty rats at an age when body weight and hyperinsulinemia peaked (165). Vaspin expression was shown to decrease with worsening of diabetes and body weight loss. Administration of recombinant human vaspin to a mouse model of diet-induced obesity improved glucose tolerance and insulin sensitivity, suggesting that vaspin may represent an insulin-sensitizing adipokine. Human vaspin mRNA was reported to be expressed in visceral and subcutaneous adipose tissue. It was shown to be regulated in a fat-depot specific manner, and to be associated with obesity and parameters of insulin resistance (166). Likewise, elevated vaspin serum concentrations were correlated with obesity and impaired insulin sensi-

tivity, whereas type 2 diabetes seemed to abrogate this correlation (167).

Much remains to be learned about the role of vaspin in glucose metabolism. Identification of vaspin's protease substrate is crucial to understand how vaspin may modulate insulin resistance.

VISFATIN/PBEF/NAMPT

Visfatin, originally isolated as a presumptive cytokine named pre-B cell colony-enhancing factor (PBEF) that enhances the maturation of B cell precursors (168), and displays nicotinamide phosphoribosyltransferase (Nampt) activity (169), was reported to be highly correlated with the amount of visceral fat in humans and in a mouse model of obesity and insulin resistance, to exert insulin-mimetic effects in cultured cells, and to lower plasma glucose levels in mice (170). Although this study was retracted in 2007 due to numerous scientific flaws, the original observation was supported by a number of subsequent studies demonstrating that plasma visfatin levels in humans correlate with obesity, visceral fat mass, type 2 diabetes, and presence of the metabolic syndrome (171–173). Furthermore, visfatin promoter SNPs were reported to be associated with fasting glucose and insulin levels, as well as type 2 diabetes (174,175). Other studies, however, did not confirm an association of visfatin and visceral adipose tissue or parameters of insulin sensitivity in humans and rodents (176–179). Recent data pointed to an important role of visfatin/PBEF/Nampt in pancreatic β -cell function. In contrast to the results of Fukahara *et al.* (170), Revello *et al.* (180) demonstrated that the extracellular form of Nampt (eNampt/Visfatin/PBEF), which is secreted through a non-classical secretory pathway, did not show insulin-mimetic effects *in vitro* or *in vivo*, but rather exhibited robust nicotinamide adenine dinucleotide (NAD) biosynthetic activity. Haplodeficiency and chemical inhibition of Nampt resulted in significantly decreased NAD biosynthesis and glucose-stimulated insulin secretion in pancreatic islets *in vitro* and *in vivo*. Con-

versely, administration of the Nampt reaction product nicotinamide mononucleotide (NMN) resulted in an amelioration of these defects.

In summary, current data suggest that adipose tissue as a natural source of eNampt/visfatin/PBEF may regulate β -cell function through secretion of eNampt and extracellular biosynthesis of NMN.

ADIPOKINE INTERPLAY

Insulin resistance should be conceptualized in a very broad manner that takes into account the interplay between nutrition, glucose, insulin and adipokines in various tissues of metabolic importance. Interactions between distinct adipokines add additional complexity to the picture (Table 1, Figure 1). Current data on adipokine interplay are rather sparse and, in part, contradictory due to examination of different *in vitro* (different cell types) and *in vivo* (different species) models.

Adiponectin and TNF- α control each other's synthesis and activity, thus creating a balanced physiologic situation (164). Overnutrition results in activation of inflammatory pathways causing a critical imbalance leading to decreased expression of adiponectin. TNF- α and IL-6 play a key role in the regulation of many adipokines. TNF- α was reported to downregulate RBP4 production in human adipocytes (181). Expression of leptin (182,183), resistin (115), and visfatin/PBEF/eNampt (184) is increased by TNF- α and IL-6. Conversely, leptin (185), resistin (116–118), and visfatin/PBEF/eNampt (186) upregulate the production of TNF- α and IL-6, suggesting that these adipokines could trigger or participate in the inflammatory process through direct paracrine and/or autocrine actions. Leptin, however, also was reported to suppress the expression of resistin and RBP4 (92,187,188), and to increase adiponectin expression in leptin-deficient ob/ob mice (188,189). Chemerin and vaspin, like adiponectin, were shown to have antiinflammatory properties. Chemerin inhibited the production

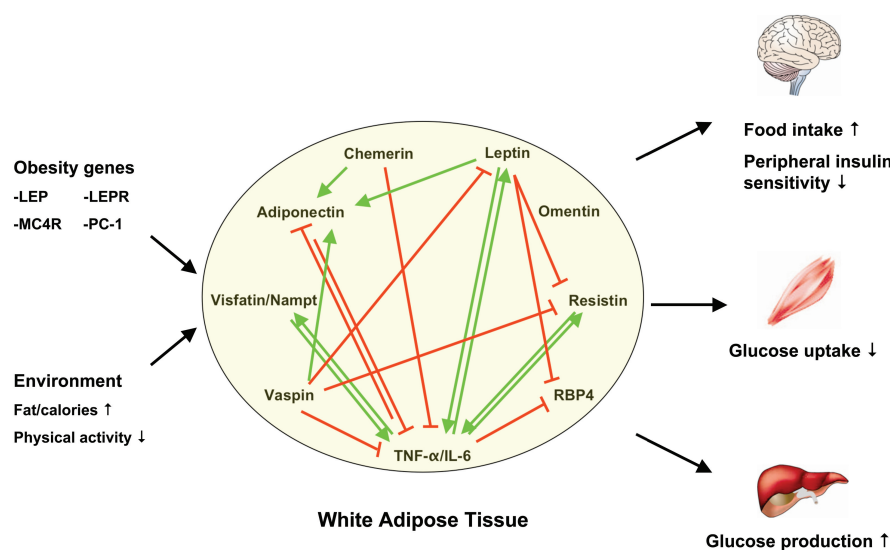


Figure 1. Obesity, adipokines and insulin resistance. Murine resistin is expressed in white adipose tissue, whereas in humans, resistin is mainly produced by peripheral-blood mononuclear cells. Green arrows depict stimulation, red lines suppression of gene expression.

of TNF- α and IL-6 by classically activated macrophages (64). Furthermore, knockdown of chemerin in 3T3-L1 adipocytes reduced adiponectin expression (63). Vaspin suppressed the expression of leptin, resistin, and TNF- α in white adipose tissue, yet increased the expression of adiponectin (165). No data have yet been reported on the interaction between omentin and other adipokines.

CONCLUSION

Obesity has reached dramatic proportions affecting more than 1 billion adults worldwide (190). The epidemic of obesity also affects children becoming overweight at progressively younger ages. Obesity is associated with an array of health problems including insulin resistance and type 2 diabetes, fatty liver disease, atherosclerosis, airway diseases, degenerative disorders, and various types of cancer. Our understanding of the pathogenesis of obesity and its metabolic sequelae has advanced significantly over the past decades. Environmental factors, such as sedentary lifestyle and increased calorie intake, in combination with an unfavorable genotype, are responsible for the epidemic of obesity. Excess visceral fat accumulation results in altered

release of adipokines, leading to CNS-mediated skeletal muscle and hepatic insulin resistance (Figure 1). Understanding of the diverse effects of distinct adipokines and the interactions between these bioactive mediators is still incomplete. Unraveling the pathophysiological roles of adipokines in obesity-induced diseases likely will result in new pharmacotherapeutic approaches.

ACKNOWLEDGMENTS

This work was supported by a grant from the Deutsche Forschungsgemeinschaft (BR 2151/4-1 to UCB).

DISCLOSURE

The authors have nothing to disclose.

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